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08/456,694

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EXAMINER: KIM, K

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DATE MAILED: ~~06~~ 12/21/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

IDS 6/1/95; Re Amend

☑ This application has been examined ☑ Responsive to communication filed on 9/29/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449. (2 page.)
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-21 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☑ Claims 1-21 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☑ Other The IDS filed 6/1/95 is duplicative to the copy previously considered in the parent 08/400,717 and are instantly made of record. As such that copy is being returned to Applicant.

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

Part III DETAILED ACTION

1. The disclosure is objected to because of the following informalities: the status of the applications cited at page 11, last line to page 12, line 20, and page 20, line 1 of the specification needs to be updated. Appropriate correction is required.

2. The disclosure at page 43, line 5 has a protein sequence which must comply to the sequence rules as set forth under 37 CFR 1.821-1.825.

3. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22-34 of copending application Serial No. 08/408,717. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims to the copending application are drawn to the particularly improved method of making vaccines of the instant claims which renders obvious the improvement in the method of making vaccines and uses thereof claimed instantly.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. Claims 1-6, 9, 10 and 12 are rejected under 35 U.S.C. § 102(b) as being anticipated by Andersson et al (1991) or Rehner et al 4,931,392.

Andersson et al teach conjugation of cyanylated dextran with CDAP to a second moiety such as EGF. See page 440. Further, Andersson et al teach the use of triethylamine (TEA) on page 440.

See column 9 for the teachings for cyanylating dextran with CDAP-BF4 and conjugation to creatine kinase of Rehner et al. Rehner et al states that the methodology of Kohn et al (1984) has been applied to make the conjugates. See column 4, lines 26-37 and column 9, lines 20-21.

7. Claims 1-6, 9, 10 and 12 are rejected under 35 U.S.C. § 102(e) as being anticipated by Handley et al 5,177,059.

Handley et al disclose conjugation of dextran with CDAP to polymyxin B. See column 5, Example 1. The reference also teaches the use of TEA at column 5, lines 6-8.

The references relied above do not particular recite the pH of the activation step (a) of Applicant's claimed invention as pH between 8-10 although the second step of coupling the activated carbohydrate to a second moiety is exemplified to be within the pH 7-9 range stated in claim 5. See column 5, lines 14-15 and col. 6, line 11 of Handley et al for the teachings

of the addition of PMB protein to the activated CHO at pH 9.0; and similar addition to the enzyme at pH 8.2 of Andersson on page 440, first column, for instance. Nevertheless, the first carbohydrate such as dextran of the prior art is added to water which is accepted in the art to have neutral pH with the addition of the organic cyanylating reagent and with drop wise addition of TEA. Therefore, the pH range of 7-9 appears inherent for the first activation step.

8. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

9. Claims 1-21 are rejected under 35 U.S.C. § 103 as being unpatentable over Dick Jr. et al (1989) or Chu et al (1983) in view of Kohn et al (1984).

Dick, Jr. et al teach cyanylation of a carbohydrate such as PRP with or without ADH linker to protein carriers effective as Hib vaccine. See pages 50-51, 86 and 90. Further, the reference teaches the disadvantages of the use of CNBr including the requirement for the extreme pH. The reference does not particularly exemplify the use of cyanylating reagents such as CDAP, CTEA or pNPC.

Chu et al (1983) teach activation of polysaccharides such as Haemophilus influenza type b (Hib), Escheria coli K100 and pneumococcal 6A polysaccharides with CNBr, attaching to spacer a adipic dihydrazide (ADH) and conjugation to immunogenic carriers such as tetanus toxoid (TT), diphtheria toxoid and hemocyanin and elicitation of an immune response

in mice. See the entire reference but in particular page 247 for conjugation procedure. However, the reference does not particularly exemplify the use of cyanylating reagents such as CDAP, CTEA or pNPC.

Kohn et al (1984) teach that other cyanylating agents such as CTEA, CDAP and pNPC are preferable over CNBr as a functionally equivalent cyanylating reagent activation of carbohydrates. See page 286. Further, the reference teaches that the TEA is used with all of the cyanylating reagents organic or otherwise. See pages 296, 298 and 302. Further, the reference teaches that CDAP is more selective cyanylating reagent than CTEA or CNBr. See page 298. Further, Kohn et al gives guidelines for the weight ratios of the cyanylating agents at generally pH of 8 with maximum coupling efficiencies at page 293, Table 3 with CNBr + TEA which process has been equated with the use of more stable form of the activation agent CTEA. See page 296, second paragraph. Further, the particular procedures are set forth on page 296, 4.1.1, with suggestions for optimizing based on desired degree of activation. See page 297, Table 4. Table 4 gives guidelines for the use of between 60mg to 360mg per 10g of polysaccharides which give approximately 2.8 to 16.8 moles per 100kg using 214 g/mole of CTEA. Sigma product No. C1028. See also pages 297-302 in particular for the teachings of the uses of CDAP and pNPC as all of CTEA, CDAP and pNPC as "excellent substitutes for the hazardous and inconvenient CNBr" for the activation of carbohydrates to immobilize biologically active molecules. See page 302, 4.4 in particular of Kohn et al.

It would have been prima facie obvious to substitute the cyanylating reagents of Kohn et al in the conjugation of the immunogenic polysaccharide conjugates of Dick Jr et al or Chu et al especially since Kohn et al teach the advantages of the milder cyanylating agents which could function equivalently to CNBr taught by Dick Jr. et al in activation of a polysaccharide for the purposes of conjugation and since Dick Jr. et al also teach that the conjugation

procedures are applicable for the affinity column matrices preparation with those for immunogenic conjugates with a carrier. See page 56 of Dick Jr. et al.

10. Claims 1-21 are rejected under 35 U.S.C. § 103 as being unpatentable over Dick Jr. et al (1989) or Chu et al (1983) in view of any one of Andersson et al (1991) or Rehner et al 4,931,392 or Handley et al 5,177,059.

The teachings of Dick Jr. et al, Chu et al, Andersson et al (1991), Rehner et al and Handley et al have been set forth above.

Further Andersson et al teach optimization of the coupling process on page 440. In particular 250 mg of Dextran having molecular weight of 20 KDa has been mixed with 250 mg of CDAP (approximately 500 moles of CDAP at 235 g/mole, Sigma Product No. C2776 to 100KDa of Dextran) with the drop wise addition of TEA; then added to 50 micro gram of EGF (approximately 1:6 ratio given the data in the reference). Dextran was used at the level of 250 mg per 25 mL or 10 mg/mL.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the method for conjugation of polysaccharide to protein taught by Andersson et al or Rehner et al or Handley et al in the methods for making the vaccine polysaccharides protein carrier conjugates of Dick Jr. et al or Chu et al because the secondary references teach the advantageous use of functionally equivalent activation of the polysaccharides with the reasonable expectation that the chemically equivalent vaccine polysaccharides of the primary references will be conjugated under milder conditions with the chemically equivalent proteins with the reasonable expectation of at least the functional equivalence of the product so formed.

11. Papers related to this application may be submitted to Group 1800 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group Art Unit 1816 Fax number is (703) 305-7939 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay K.A. Kim, Ph. D. whose telephone number is (703) 308-3881. The examiner can normally be reached on Monday-Thursday from 7:00 AM-4:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on (703) 308-3973.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

June 18, 1996

KAY K. A. KIM, PH.D.
PRIMARY EXAMINER
GROUP 1800